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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

EINSMANN, JULIET CAROLINE

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 01/31/2003

26

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/429,003

Applicant(s)

SHARMA ET AL.

Examiner

Juliet C Einsmann

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2002 and 26 July 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 37,39-43,45-52 and 56-94 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37,39-43,45-52 and 56-94 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 19.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response applicant's correspondences submitted 7/26/02, paper number 24 and 11/21/02, paper number 25. In paper number 24, claims 38, 44, and 53-55 were cancelled, and claims 37, 39, 47, 56, 57, 58, 59, 60, 61, 62, 64, 65 were amended and claims 66-94 were added. A declaration was submitted in paper number 25. Claims 37, 39-43, 45-52, and 56-94 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

2. The 1449 filed 11/5/01 has been considered. An updated copy of the 1449 is included with this office action indicating that all of the references were considered.

Claim Rejections - 35 USC § 112

3. Claim 37, 39-43, 45-52, and 56-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of obtaining isolated selected mRNA species useful for diagnosing or identifying a disease or condition wherein the mRNA is isolated from cells that are obtained a part of an organism distant to the area of disease, does not reasonably provide enablement for methods of obtaining isolated selected mRNA species useful for diagnosing or identifying a disease or condition wherein the mRNA is isolated from cells that are obtained from a part of said organism distant to the area of said disease and have not contacted the area of said disease from a part of an organism distant to the area of disease.

Art Unit: 1634

Furthermore, while being generically enabled for methods of obtaining isolated selected mRNA species useful for diagnosing or identifying a disease or condition wherein the mRNA is isolated from cells that are obtained a part of an organism distant to the area of disease, the specification is not enabling for methods in which the disease is Alzheimer's disease in particular (newly added claims 78-94). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to methods of obtaining isolated selected mRNA species "useful for diagnosing or identifying a disease or condition." The claims are also drawn to methods for diagnosing patients using said the products identified by the methods for obtaining isolated selected mRNA species. Some of the claims recite that the probes will be useful for diagnosing specific diseases such as Alzheimers disease and cancer (stomach, lung, breast, prostate, bowel, and skin). The claims specifically recite the isolation of mRNA from cells of organisms that have a disease and the isolation of mRNA from healthy organisms. In many of the claims, the cells are required to have "not contacted the area of said disease and are obtained from a part of said organism distant to the area of said disease (claims 37, 39-43, 45-52, and 56-77)," while others require only that the "cells are obtained from a part of said humans distant to the area of said disease (Claims 78-94)."

The specification provides a single working example wherein mRNA is isolated from cells that did not come in contact with an area of disease and were obtained from an area distant from the area of disease is isolated and used to create diagnostic gene transcript patterns. Particularly, in example 6, a differential expression type methodology is used to analyze

Art Unit: 1634

infection for a fungal pathogen in Norway spruce. A root fungus, *Pythium dimorphum*, is introduced to Norwegian spruce. Samples mRNA is collected from samples of the needles of the infected plants and control plants, reverse transcribed and amplified using primers specific to transcripts that were differentially expressed in plants that were infected with the fungus or spruce that were challenged with "other types of stress (specification page 38)." The amplified cDNA samples were hybridized to probes for the differentially expressed transcripts.

Hybridization patterns are shown in figure 2, where there is a clear difference in the pattern from the needles of the tree stressed with the fungus versus the control needles (see second page of Figure 2, bottom two graphs). However, this example does not sufficiently demonstrate that this method is diagnostic of the particular condition of the fungal pathogen, because it does not differentiate between the determination that one can determine that the spruce was STRESSED versus having a particular disease. The example states that some of the probes used are not specific to the disease but of are particular to stressed plants.

The remaining examples provided in the specification are largely prophetic, and do not provide clear data which indicates the functionality of this invention. Examples 1 and 2 provide direction as to the use of this invention for the diagnosis of Alzheimer's disease and senile dementia, however, they do not provide the transcript patterns necessary or any specific probes useful for the diagnosis. Example 4 appears to provide the use of a differential expression methodology for the production of a diagnostic transcript pattern for Arabidopsis, however, the specification does not provide any data as to the disease being studied. Thus, it is unclear if the disease is systemic or localized. It is not clear if the tissue samples taken were from the location of the disease or from some other disease. The example states that it is leaves that are sampled,

Art Unit: 1634

but it gives no indication if it was healthy leaves or diseased leaves. Example 5 provides a prophetic example of humans, merely stating that results would be expected to be “similar to those in figure 1.” The result in figure 1 appear to be hypothetical results.

The prior art provides extensive guidance as to the use of differential expression methodology for the identification of probes useful for the detection of disease (see, for example, Graber *et al.* or Ditkoff *et al.*, cited in previous actions). With regard to the identification of nucleic acid probes which are isolated from cells have not come in contact with the area of disease, the prior art is silent. Ralph *et al.* (US 6190857) provide probes which identify genes that are expressed in the peripheral blood of individuals with prostate or breast cancer compared to normal individuals. Ralph *et al.* teach that their invention is directed towards detecting a response of circulating leukocytes to the disease site (Col. 5), thus suggesting that the basis of their invention is that the cells have in fact come in contact with the disease site. Zhi-Xin *et al.* (Zhongguo Zhongliu Linchuang (1996) Vol. 23, No. 4, pp. 243-246) teach that IL-2R expression in peripheral blood mononuclear cells is closely associated with the presence of tumor metastasis in lung cancer patients. Like Ralph *et al.*, Zhi-Xin *et al.* teach that the expression they are detecting is a result of the cells coming in contact with the cancer cells (see page 10 of the translation of Zhi-Xin *et al.*

The prior art does not provide any guidance with regard to the identification of nucleic acid probes which are isolated from cells that originate from a location distant from the point of disease for diseases in other types of cancers or other types of diseases. The diagnosis of Alzheimer's disease is quite difficult, and the confirmation of such a diagnosis is currently only possible post-mortem. Buckland *et al.* studied levels of amyloid precursor protein mRNA levels

Art Unit: 1634

in blood cells of patients with Alzheimer's disease but did not observe any differences between disease and control groups (Molecular Brain Research, 1993). Sato et al. showed that Cu, Zn superoxide dismutase mRNA levels were higher in patients with AD than in controls in skin fibroblast samples (Acta Neurol Scand 1995;91:165-168). However, they do not suggest any other transcripts in skin fibroblasts that might be useful for the diagnosis of AD, and all of the current claims require that at least two diagnostic transcripts be examined. The identification of such other transcripts is highly unpredictable.

Neither the specification nor the prior art provide any guidance as to how to identify cells in a sample that have "not come in contact with the area of disease," except for the case wherein the area of disease is the brain where the blood-brain barrier would prevent brain cells from leaving the area of the brain intact. For example, within the instant claim set are dependent claims that recite that the cells are blood cells and the disease is cancer (stomach cancer, for example). Yet the specification does not provide any guidance as to how one would ascertain which blood cells in a sample have come in contact with the possible stomach tumor and which have not. This identification is highly unpredictable since they would ostensibly all be in the same blood sample.

While level of skill in the art (i.e. a PhD in biochemistry) is quite high, but the unpredictability associated with identifying isolated selected mRNA species which are obtained from cells which have not contacted the point of disease and are useful for the detection of diseases is higher. The human blood, for example, expresses hundreds of thousands of different transcripts, and which of these particular transcripts would be useful for the detection of any particular disease is highly unpredictable. The determination of such an association requires

Art Unit: 1634

extensive laboratory work, as is exemplified by the teachings of Ralph *et al.* In order to enable the instant claims to their current breadth, some showing that the method functions for a representative number of diseases would be required. Since the claims embrace diagnostics for any disease or condition in any eukaryote, a representative number would have to include different eukaryotes and a variety of diseases. No such showing is provided in the instant specification.

Because of the lack of working examples, the high level of unpredictability in the art, the lack of guidance provided in the specification or the art, and the high level of experimentation necessary to practice the claimed invention, it is concluded that undue experimentation would be necessary to practice the claimed invention.

RESPONSE TO REMARKS

The prior art rejections and rejections under 112 1st paragraph for new matter and written description have been withdrawn in light of Applicant's amendments to the claims.

The rejection under 112 1st paragraph has been modified to more appropriately characterize example 6, and to address the amendments to the claims. Applicant's remarks filed in paper 24 and the declaration filed in paper number 25 are addressed herein insofar as they are relevant to the remaining rejection.

Applicant points out that example 6, which is not speculative can be used "diagnostically to determine the state of the plant from which the cell was derived (p. 22 of paper 24)." The examiner agrees, in part. The example demonstrates that a diseased plant generates a different hybridization profile to particular stress markers than a healthy plant when the mRNA is isolated from cells that did not come in contact with the area of disease (here the roots versus the

needles). However, this is not a diagnosis, per se, wherein the example demonstrates that one could determine what disease the plant harbors. Instead, the example demonstrates that the stressed plant demonstrates a differential hybridization pattern against probes specific for genes that were known to be differentially expressed in “stressed plants.” Applicant has not demonstrated a pattern that can be used to diagnose a specific disease, but that demonstrates that disease is present. Furthermore, even if this were persuasive for this particular root fungus in Norwegian spruce, the claims are drawn to the detection of disease in ANY organism, which includes all possible diseases in all possible organisms, an extremely large genus. These results are not sufficient to support such a claim for the reasons discussed in the rejection.

The declaration under 37 CFR 1.132 filed November 21, 2002 is insufficient to overcome the rejection of the pending claims based upon 112 1st paragraph, lack of enablement, as set forth in this and the last Office actions. The declaration is presented in two parts, one wherein a gene transcript pattern and diagnostic are provided for Alzheimer’s disease and one for Breast cancer.

The Alzheimer’s disease example will be considered first. The data provided in the declaration is not sufficient to establish that 10 or more differentially expressed transcripts were observed in light of the fact that the sample sizes were small (6 diseases individuals versus 6 controls) and no statistical analysis is given of the differentially expressed genes. The figure provided is a bar graph in which most of the bars are very close in size for the normal and diseased samples. All of the claims require that at least two or more differentially expressed genes be observed, and many of the claims require 10 or more. These data are not sufficient to establish this level of differential gene expression. Furthermore, the validation process is not sufficient to determine that the differential expression pattern is particular to Alzheimer’s disease

Art Unit: 1634

because there is no other “diseased control” present. So it is not possible to determine whether the diagnosis would be specific to Alzheimer’s disease or merely to a “stressed” state. For these reasons, the declaration is not sufficient to support the claims for Alzheimer’s disease in particular or the claims to the diagnosis of disease in general.

The second experiment in the declaration involves breast cancer. Again, no data or statistical validation is provided to confirm that even ten genes are differentially expressed between the diseased and control patients, nor does the experiment validate the ability of the method to diagnose breast cancer versus a different disease. In both cases, no data is given as to which genes are being differentially expressed or at what levels, and thus it is impossible to determine from the examples, if, for example, the same genes are being differentially expressed in Alzheimers samples and breast cancer samples.

Furthermore, the experiment does not address the question of how to determine whether or not the cells being tested have “come in contact with the area of disease.” These methods, like the methods used by Ralph et al. are using whole blood samples. However, Ralph et al. teach that they would be detecting blood that has come in contact with, for example a breast tumor, while Applicant’s claims require that the blood has not come in contact with the tumor. It is unclear how to determine, from the blood sample, which cells have come in contact with the tumor.

It is also noted that the breadth of the claims encompass the detection of disease via the use of a variety of body fluids or body parts, even, yet these two examples only demonstrate blood, which is a narrow embodiment.

Art Unit: 1634

Thus, even in view of all of the evidence of record, the rejection is maintained and newly set forth for the added claims.

Conclusion

4. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Juliet C Einsmann
Examiner
Art Unit 1634

January 24, 2003



JEFFREY FREDMAN
PRIMARY EXAMINER